nomas, and because of this, they are usually at an early stage at diagnosis. It is postulated that unopposed estrogen also leads to hyperprolactinemia in about 25% and galactorrhea in 13% of women with the polycystic ovary syndrome.

Other long-term health consequences of the polycystic ovary syndrome include a markedly increased risk for cardiovascular disease, with an estimated 11-fold increased risk of myocardial infarction between the ages of 50 and 61 years. Recent preliminary reports also suggest an increased risk of breast cancer in women with this syndrome.

Because the cause of this common syndrome is unknown, it is not surprising that there is no specific treatment for it. It is clear that because of the many serious health problems attributable to the polycystic ovary syndrome, the management of a patient with this condition requires attention not just to the immediate complaints, but also to the prevention of long-term sequelae. Patient education is of paramount importance if long-term compliance is to be achieved.

In Europe, the antiandrogen cyproterone acetate is one of the most commonly employed treatments of hirsutism associated with the polycystic ovary syndrome. It has progestogenic activity and is combined with ethinyl estradiol in a combined oral contraceptive (Diane). In North America, cyproterone acetate is unavailable, and spironolactone, a mineralocorticoid antagonist with androgen receptor-blocking activity, is used extensively. Flutamide, another antiandrogen, and finasteride, a specific 5α-reductase inhibitor, have been reported to have good effect in the treatment of hirsutism associated with the polycystic ovary syndrome. For the optimal efficacy of spironolactone and flutamide treatments, these drugs are often prescribed with a combined oral contraceptive pill. If oligomenorrhea or amenorrhea is present, the addition of an oral contraceptive pill will also eliminate the increased risk of endometrial cancer. Maximal effects with any of the above forms of therapy take in excess of four months to manifest clinically. Hence, it should be recommended that patients wait at least this long to allow the cessation of new terminal hair growth before undergoing physical forms of hair removal to remove any pretreatment unwanted hair.

Correcting obesity can further augment the therapeutic results. In one long-term noncontrolled prospective study of obese women with the polycystic ovary syndrome, a 5% reduction in body weight led to a decrease in serum insulin and free testosterone levels and a rise in SHBG levels.[3] This group was also substantially more likely to have improvement in reproductive function, as documented by more regular menstrual cycles and improved pregnancy rates, than those women who lost less than 5% of their baseline weight.

The differential diagnosis of hirsutism includes a number of other conditions. Unless the physician specifically explores the possibility of each of these, the correct diagnosis will not be made. For example, treating a woman with the complaints of hirsutism, obesity, and menstrual irregularity with oral contraceptives because of the presumed diagnosis of the polycystic ovary syndrome would not be appropriate if she has the Cushing's syndrome. In this issue of the journal, Roland Sakiyama, MD, presents an overview of the approach to patients with hirsutism.[4] The possible causes, necessary diagnostic evaluation, and treatments are covered in a systematic manner. It is fortunate that most causes of hirsutism are relatively benign. Steroid-secreting tumors are uncommon, even in a reproductive endocrinology clinic setting.

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The Search for Viable Myocardium

LEFT VENTRICULAR FUNCTION is among the most important determinants of long-term prognosis in patients with coronary artery disease.[1] It is now apparent that left ventricular dysfunction does not always represent an irreversible process, as was once thought, but may be reversible, at least in part, in a large subset of patients with coronary artery disease. Left ventricular performance may be reduced on the basis of regionally ischemic, stunned, or hibernating myocardium rather than fibrosis from previous myocardial infarction. The detection of reversibly dysfunctional myocardium is clinically relevant because regional and global left ventricular function in such patients may improve substantially after revascularization. A third or more of patients with chronic coronary artery disease and left ventricular dysfunction manifest a substantial improvement, and even a return to normal, of ventricular function after bypass surgery or angioplasty.[2] This improvement in systolic function, in turn, translates into enhanced survival. Thus, as discussed in the review by Birnbaum and Kloner elsewhere in this issue of the *Journal*,[3] the recognition that many patients with coronary artery disease and left ventricular dysfunction may not have irreversibly damaged ventricles, and the development of cost-effective imaging techniques to

identify viable myocardium, have important clinical implications.

Stunning and Hibernation

Two distinct pathophysiologic processes, myocardial stunning and myocardial hibernation, have been proposed as the mechanisms for reversible contractile dysfunction in humans, and these complex processes have been described in detail and in an understandable manner in Birnbaum and Kloner's review.[3] Stunning represents contractile dysfunction after an episode of myocardial ischemia, resulting from ischemic injury with possible superimposed reperfusion injury.[4] Hibernation, on the other hand, does not represent an injury but is thought to be an adaptive, protective mechanism by which the myocardium inhibits its contractile elements in the setting of sustained reductions in blood flow to match its oxygen demands with the reduced oxygen supply.[5] It is important to note, however, that the distinct definitions of these terms, in black and white on the printed page, become indistinct margins with important shades of gray in many clinical situations. For example, acute left ventricular dysfunction after reperfusion therapy for myocardial infarction could represent myocardial stunning if the infarct-related artery is widely patent, but could also represent acute hibernation as an adaptive response to persistent hypoperfusion when the previously occluded infarct-related artery has been opened but a residual high-grade, flow-limiting stenosis remains.

Similarly, chronic left ventricular dysfunction that improves after revascularization is usually thought to represent myocardial hibernation, and the improvement in function is considered the result of improved blood flow under resting conditions.[5] In some situations, however, blood flow may be normal at rest in dysfunctional myocardium, and sustained contractile dysfunction results from repeated episodes of reversible ischemia and repetitive postischemic stunning.[6] This situation will also improve only if revascularization or other interventions are performed to abolish the ischemic episodes. In this situation, revascularization does not improve blood flow at rest, as in the case of hibernation, but improves vasodilator reserve during stress, thereby reducing the extent and magnitude of reversible ischemia. This is one form of stunning in which myocardial dysfunction will not improve spontaneously, and so spontaneous improvement in function is not a prerequisite for stunning, as suggested by Birnbaum and Kloner.[3]

It is also likely that both hibernation and repetitive stunning may occur together in the same patient and perhaps even in the same myocardial region. A myocardial region that is hibernating at rest, with a critical balance of reduced perfusion and reduced function, may develop ischemia during exercise, followed by a process of postischemic stunning superimposed on the baseline hibernating state.[7]

Thus, the clinical distinction between hibernating myocardium, stunned myocardium, or a combination of these processes is difficult and often impossible. Luckily, this distinction is also of limited importance. Instead, the clinically important issue is the understanding that left ventricular dysfunction in many patients with coronary artery disease is not an irreversible process related to fibrosis but may represent a reversible process that will improve if recognized and if the patients are revascularized. Noninvasive methods have evolved during the past decade to assess myocardial viability and are ideally suited for this purpose. These include methods to study metabolic activity, membrane integrity, and inotropic reserve.[2,7,8]

Identifying Viable Myocardium

Positron emission tomography. Positron emission tomography (PET) has emerged as a promising method for demonstrating viable myocardium in patients with compromised left ventricular function. Myocardial viability is identified by PET on the basis of intact metabolic activity in regions of severely underperfused and dysfunctional myocardium. The most extensive experience thus far has been achieved using fludeoxyglucose F 18 (^{18}FDG) as a marker of regional exogenous glucose use in such hypoperfused regions. In particular, a pattern of enhanced ^{18}FDG uptake in regions with reduced perfusion (called the ^{18}FDG-blood flow "mismatch") indicates that viable tissue has preferentially shifted its metabolic substrate toward glucose rather than fatty acids or lactate.[8] The finding of preserved metabolic activity in myocardial regions with reduced blood flow has been demonstrated in a total of six studies, involving 146 patients, to be an accurate clinical marker with which to distinguish viable myocardium from myocardial fibrosis, with positive and negative predictive accuracies of 82% and 83%, respectively, for predicting which dysfunctional regions will manifest improved function after revascularization.[7] Thus, PET appears to yield excellent viability information.

Thallous chloride Tl 201 imaging. The requirements for cellular viability include intact sarcolemmal function to maintain electrochemical gradients across the cell membrane, as well as preserved metabolic activity to generate high-energy phosphates. These processes also require adequate myocardial blood flow to deliver substrates and wash out the metabolites of the metabolic processes. As the retention of thallium (thallous chloride Tl 201) with time is an active process that is a function of cell viability and cell membrane activity, as well as blood flow, thallium should in theory be taken up and retained by myocardial regions that also retain ^{18}FDG and other metabolic tracers.

The thallium protocols using single-photon emission computed tomography (SPECT), which have been best adapted for assessing myocardial viability, are as follows: thallium reinjection imaging, in which imaging is repeated after a small additional dose of thallium is administered at rest after a period of redistribution following stress imaging,[9] and thallium imaging without exercise using a rest-redistribution protocol.[10] It has been shown in 13 SPECT studies, totaling 378 patients, that these protocols each achieve a positive predictive accuracy of 69% and negative predictive accuracies of 89% and 92%, respectively.[7] In each of these protocols, both defect reversibility and severity of the thallium defect are

important markers of viable myocardium, and the positive predictive value can be enhanced considerably by performing a quantitative analysis of defect severity.

Technetium Tc 99m sestamibi imaging. Unlike thallium, technetium Tc 99m sestamibi does not redistribute appreciably after being administered during exercise or at rest. Thus, ^{99m}Tc-sestamibi may have inherent disadvantages relative to thallium for assessing viability. This concept is supported by studies showing that rest-exercise ^{99m}Tc-sestamibi imaging underestimates viable myocardium in patients with chronic coronary artery disease and left ventricular dysfunction compared with exercise-redistribution-reinjection thallium imaging.[11] Recent data suggest, however, that quantitative analyses of regional ^{99m}Tc-sestamibi activity after a resting injection of the tracer may increase the accuracy of sestamibi for identifying viable tissue.[10] Although these results are promising, this agent remains more of an investigational agent than a preferred agent for this purpose.

SPECT metabolic markers. The role of SPECT imaging using metabolic tracers has been less extensively studied compared with the large number of studies using thallium or ^{99m}Tc-sestamibi. Technetium-based or iodinated fatty acids have been studied in preliminary trials and appear promising.[12] In addition, the ability to image PET tracers, such as ^{18}FDG, using high-energy collimators, is a new and unique application of current SPECT technology that may allow a more routine use of PET metabolic tracers for assessing viability.[13] The accuracy of SPECT imaging of PET tracers for this purpose has not been extensively evaluated to date.

Dobutamine echocardiography. Previously ischemic, stunned myocardium maintains contractile reserve that can be identified following the administration of inotropic agents such as dopamine, isoproterenol, and dobutamine, as well as by postextrasystolic potentiation. Low-dose dobutamine infusion to enhance regional systolic wall thickening during echocardiography has recently been proposed as a clinical method to assess contractile reserve and has been applied successfully to patients after thrombolytic therapy for acute myocardial infarction and also to patients with chronic left ventricular dysfunction.[14] The results of 15 studies of chronic coronary artery disease, involving a total of 402 patients, indicate that this method predicts the recovery of left ventricular function after revascularization with a predictive accuracy virtually equivalent to that achieved using PET protocols, with positive and negative predictive accuracies of 83% and 81%, respectively.[7]

Clinical Implications

The identification of viable myocardium has become an area of intense interest for several reasons. Among these is the unique potential of nuclear cardiology techniques to distinguish viable regions on the basis of perfusion, cell membrane integrity, and metabolic activity and the ability of dobutamine echocardiography to assess regional inotropic reserve. Although the available data imply that each of these methods has similar diagnostic accuracy, larger scale studies comparing the use of PET, thallium, and dobutamine echocardiography are required in patients undergoing revascularization to determine the relative efficacies of these methods in identifying viable myocardium.

The evolving PET data indicate that the identification of viable myocardial tissue in patients with coronary artery disease and left ventricular dysfunction has several important, clinically relevant implications. First, the augmentation in regional systolic function after revascularization, as predicted by ^{18}FDG-blood flow mismatch, results in a substantial and predictable increase in the global left ventricular ejection fraction.[8] This increase in left ventricular ejection fraction after revascularization in patients with viable myocardium appears to translate into an improvement in the prognosis.[2,7,8,15] Finally, the improvement in left ventricular function after revascularization in patients with viable myocardium is also associated with a considerable lessening of symptoms of congestive heart failure.[15] These survival and function results have important implications in the management of patients with congestive heart failure because coronary artery disease accounts for as much as 80% of cases of heart failure in this country. Although more definitive data are required before full conclusions can be drawn, these data suggest that patients with impaired left ventricular function who have extensive evidence of underperfused but viable myocardium are a subgroup of patients who may have substantial improvement in outcome if identified and treated with myocardial revascularization. These patients appear to have the potential for improved left ventricular function, decreased symptoms, and improved survival. Whether these clinical outcome data derived from PET studies can be generalized to viability markers obtained from thallium imaging or dobutamine echocardiography awaits further study.

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